

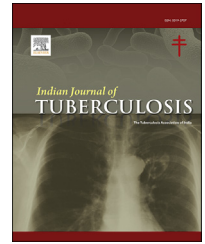


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Original article

Non-adherence to anti-tubercular treatment during COVID-19 pandemic in Raipur district Central India

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ABSTRACT

Background: Non-adherence is major factor in failure of any drug regimen. The significance of non-adherence is so much that WHO states that increasing the effectiveness of Adherence Interventions may have far greater impact on health of population than any improvement in specific medical treatments. Incidence of non-adherence to Anti Tubercular Treatment (ATT) usually ranges from 8.4% to 55.8%. This study aims to find out the reasons of Non-adherence to ATT in patients receiving anti-tubercular treatment at DIRECTLY OBSERVED TREATMENT SHORTCOURSE (DOTS) Centre at District Tuberculosis Centre (DTC), Kalibadi, Raipur during COVID-19 pandemic.

Methods: A cross sectional study was conducted at Department of Pharmacology, Pt. JNM Medical College and DTC Kalibadi Raipur. 55 Patients taking ATT fulfilling inclusion and exclusion criteria were interviewed using structured questionnaire. The data obtained was analysed to know causes of non-adherence.

Results: Study was carried out between March & April 2020. In our study, 80% subjects were male and 20% were female. The main reasons for Non-adherence were Side-effects of drug in 36% cases, missing medication intentionally in 34% cases, lack of encouragement by family members in 32% cases, patient's unawareness of consequences of skipping medication in 25% cases, unaware of treatment duration in 22%, not feeling any change, forgetting to take medication, and burden of concomitant medication besides ATT, each in 20% cases, 13% cases had difficulty in procuring medication due to lockdown, 5% cases did not go to collect their medicine due to fear of contracting COVID-19 infection.

Conclusions: Our study shows reasons for Non-adherence are multi-factorial with drug side-effects & intentionally skipping medication being major factors.

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1. Introduction

TB is a major health concern.¹ Globally, an estimated 10 million people fell ill with TB in 2018, accounting for approximately 1.5 million deaths in 2018. These include 251,000 HIV positive patients,² thus making TB the leading cause of death in such patients. TB affects people of all age groups and both the sexes; however, incidence is maximum in men over 15 years of age.²

INDIA is a hot bed of TB with approx. 2.69 million new cases in 2018,² 92,000 out of those being HIV positive.² Poor adherence is very common despite multiple interventions aimed at improving treatment completion. Non-adherence not only leads to treatment failure and poor treatment outcome³ but also is a major factor in drug resistance leading to emergence of MDR and XDR TB strains.⁴

1.1. Classification of TB⁵

TB can be classified in multiple ways depending on the anatomical site, history of treatment or drug resistance.

1.1.1. Based on anatomical location

Pulmonary TB—A case of TB involving the lung parenchyma or tracheo-bronchial tree is classified as Pulmonary TB,

Extra-Pulmonary TB—While case of TB involving pleura, lymph nodes or other body parts like intestines, bones, brain etc. is classified as Extra-Pulmonary TB.

1.1.2. Based on history of treatment⁵

New case—A patient who has never taken Anti-tubercular treatment in his life or one who has taken anti-TB treatment for less than 1 month is classified as a NEW CASE.

Previously treated cases—They have previously taken Anti-TB medication for more than 1 month and are of following types:

1. Recurrent case—A case successfully treated in the past but is subsequently found to be a confirmed case.
2. Treatment after failure—Previously treated case whose failed at recent most treatment.
3. Treatment after loss to follow up—Earlier treated patient lost in follow up who is now a confirmed case.
4. Others—They have been treated previously, but the outcome of their recent most treatment is unknown.
5. Transferred in case—A patient coming to a TB unit after having received treatment from other TB unit.

1.1.3. Based on drug resistance⁵

1. Mono-Resistance (MR)—Patient with resistance to any 1 1st line TB drug.
2. Poly Drug resistance (PDR)—Patient with resistance to more than 1st line TB drug other than both INH & RIFAMPICIN.
3. Multi Drug Resistance (MDR)—Resistance to both INH & RIFAMPICIN with or without resistance to other 1st line drugs.

4. Extensive Drug Resistance (XDR)—An MDR case additionally resistant to fluoroquinolones & 2nd line of injectable TB drugs like kanamycin or amikacin.

1.2. Drug regimen⁵

The Indian TB National Strategic Plan (NSP) 2017–2025⁶ is the plan produced by the government of India (GoI) which states that even though India is engaged in TB control activity for >50 years yet it continues to be India's health crisis. It kills approx. 4,80,000 Indians every year, approx. 1400 per day.

Type of TB Case	Initiation phase	Continuation phase
New	HRZE (2 Months)	HRE (4 Months)
Previously treated	HRZES (2 Months) + HRZE (1 Months)	HRE (5 Months)

While diagnosing, the patient first has to be categorised as having Pulmonary or Extra Pulmonary Tuberculosis. All new TB patients in India should receive an internationally accepted first line regimen (A regimen is the prescribed course of treatment in the case of TB drugs).

For new patients the intensive phase should consist of eight weeks of the drugs isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) the continuation phase should consist of 3 drugs Isoniazid (H), Rifampicin (R), Ethambutol (E) given for another 16 weeks, this is alternatively written as 2HREZ/4HRE, there will be no need for extension of the continuation phase.⁶

The drug should be given according to the body weight of the patient. There are 4 weight band categories, under the new daily regimen TB patient will be given fixed dose combinations (FDC). FDC's are thought to prevent acquisition of drug resistance due to monotherapy which may occur with separate drugs. The number of tablets to ingest is smaller and thus encourage patient's adherence. FDC have equivalent efficacy to single pill and is more acceptable to patients. Standard regimen for new TB patients is 2 months HRZE and 4 months of HR daily dosing.

The National Strategic Plan 2017–2025 aims at rapidly ending the TB epidemic in India. NSP envisions a TB free India with zero death and disease. The goal of NSP is elimination of TB in India by the year 2025. The approach of NSP is based on Detect-Treat-Prevent-Build model.⁶

Detect—First and foremost there is need for early detection of all TB cases.

Treat—This is followed by not only treatment with appropriate drugs and regimen but also providing the patient with financial and nutritional support.

Prevent—In addition to all this there is focus on active case finding and contact tracing to prevent new cases.

Build—Lastly it stresses on management & upgradation of financial systems of TB control program.⁶

For the treatment to work all the medicines must be taken as per standard drug regimen. Drug side effects are a major

determinant to maintain patient compliance & adherence. Side-effects of ATT range from minor symptoms like nausea, vomiting, weakness, discolouration of urine to serious side effects like hepatotoxicity, peripheral neuropathy, changes in colour vision etc. In case treatment is interrupted or stopped early, failure can happen. This might also lead to development of drug resistant TB. Therefore, it is imperative to find the factors leading to non-adherence in tuberculosis patients in order to make strategic moves in countering TB in India.

2. Method

A cross sectional study was carried out after ethical clearance from institutional ethical committee at DTC, Kalibadi, Raipur. 55 Patients who were fulfilling the inclusion criteria were enrolled for the study. A written informed consent was taken and they were subjected to structured questionnaire. The data obtained was tabulated and subjected to statistical analysis.

2.1. Study design

A Cross sectional observational study of 8 weeks from 1st March 2020 to 30th April 2020 was conducted in Department of Pharmacology, Pt. JNMMC, Raipur and DTC, Kalibadi, Raipur. The institutional ethical committee approval was taken before study with reference no. 2020/198.

2.2. Enrolment of patient

Patient were selected with due consent from institutional ethics committee and also from the patient explaining to them the purpose of study and utility of data obtained from them. In case of a minor, consent is obtained from their parents.

2.3. Inclusion criteria

- Patients Taking Anti Tubercular Treatment at District TB Centre, Kalibadi, Raipur for minimum one month.
- Patients in age group of 15–75 years.
- Those who missed at least 3 doses in a week.

2.4. Exclusion criteria

- Psychosis
- Previously Treated Patient
- Active COVID infection.

2.5. Questionnaire

- Do you know how long will your treatment last?
- Are you aware of the dangers of skipping/stopping your treatment without doctor's advice?
- Do you feel any change (either positive or negative), ever since you started the treatment?
- Is there adequate supply of medicines at your DOTS Centre?
- Do your family members encourage you to continue taking your medicines?

- Do you sometimes, intentionally skip your medication? if yes, then what's the reason?
- Besides forgetting, is there any reason for you to miss your treatment?
- How often you have difficulty remembering to take your treatment?
- Besides att, are you taking any other medications?
- Did you have any trouble in procuring medication during COVID-19 pandemic?

2.6. Stat analysis

Sample size Can be estimated using the following formula:-

$$n = \frac{z_{1-\frac{\alpha}{2}}^2 (1 - P)}{d^2} \quad (1)$$

where P = anticipated proportion, d = absolute precision required on either side of proportion, p and d are expressed in fractions, z is a constant, its value for a 2 sided test is 1.96 for 95%.

3. Result

Our study was carried out in month of March & April 2020 with the sample size of 55 subjects. Out of 55 subjects 44 (80%) were males and 11 (20%) females.

In our study we found that the single largest factor responsible for non-adherence is drug side effects with 36% patient affirming it. Side effects in the form of nausea, vomiting, abdominal pain, generalised weakness, headache, itching skin rash, etc. make it difficult for the patient to adhere to the regimen, often resulting in skipping or stopping of treatment. Detailed information can be found in [Table 1](#), [Graph 1](#).

35% of patients in our study intentionally skipped medication.

32% of all patients cited lack of family support as the reason for non-adherence to medication.

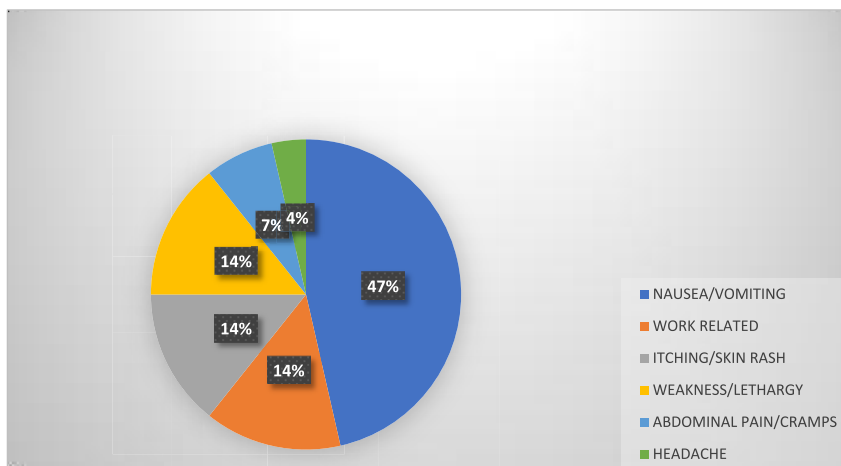
25% of the patients were unaware of the consequences of stopping the treatment midway without doctor's advice.

Table 1 – Drug side effects.

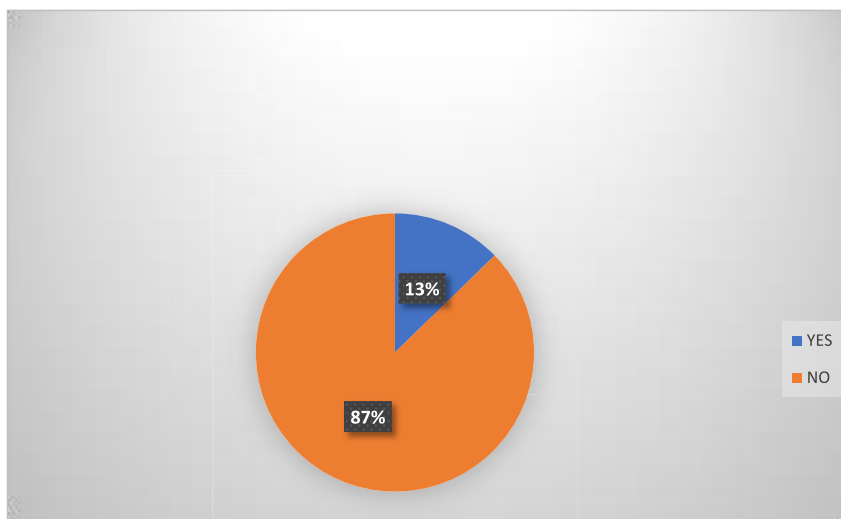
Drug side-effects	Number of patients (percentage)
Nausea/Vomiting	13 (47%)
Itching/Skin rash	4 (14%)
Weakness/Lethargy	4 (14%)
Abdominal pain/Cramps	2 (7%)
Headache	1 (4%)

Table 2 – Difficulty in procuring medication due to lockdown.

Difficulty in procuring medication due to lockdown	Number of patients (percentage)
Yes	7 (13%)
No	48 (87%)



Graph 1 – Shows percentage wise distribution of drug side-effects



Graph 2 – Shows difficulty faced in procuring medication due to lockdown.

22% patients were unaware of duration of their treatment plan which can range from 6 to 9 months.

20% of total patients were unresponsive towards the treatment and said that they didn't felt any change either positive or negative ever since the initiation of treatment. 20% of the patients forget to take Anti-tubercular medicines due to co-medications for Diabetes, Hypertension, etc.

13% of patients had difficulty in procuring medication due to commutation problem in lockdown period [Table 2](#), [Graph 2](#).

5% of patients did not contact healthcare facilities due to fear of catching COVID-19 infection [Table 3](#), [Graph 3](#).

main reasons cited for the same are drug side effects, forgetting to take medication. Being away from home, lack of social family support, low socio-economic status of the patient, poor communication between patient and health care provider. The findings of our study ([Table 4](#)) are consistent with previous studies done on the same topic elsewhere in Ethiopia, Asia and Global annual TB reports published by WHO.^{8,9}

While previous studies concentrated more on percentage of non-adherence, our focus was on finding the quantitative as well as qualitative distribution of the factors responsible.

Table 3 – Problem in collecting medication due to COVID-19 fear.

Did not collect medication from DOTS centre for fear of contacting COVID-19 infection	Number of patients (percentage)
Yes	3 (5%)
No	52 (95%)

4. Discussion

As per previous studies done earlier nationally as well as internationally the rate of Non-adherence to Anti Tuberculosis treatment in India is very high approximately 50%⁷ The

Table 4 – Reasons for non-adherence.

Reasons of non-adherence	Percentage of patients
Drug side-effects	36
Intentionally skipping	35
Lack of family support	32
Unaware of consequences of treatment interruption	25
Not feeling any change	20
Forgetfulness	20
Taking other medicines	20
Difficulty in procuring medication due to lockdown	13
Did not collect medication from DOTS centre for fear of contacting COVID-19 infection	5

The success outcome of any drug regime depends upon the patient compliance and earnest adhesion to the prescribed drug regimen. As compared to the developed economies the medical adherence is found to be low in developing countries.³

Non-adherence to TB regimen study carried out in various countries over one month was found to be 20.8% in Southern Ethiopia, 25% in Uganda, in Kolkata India 40.55% and Jiangsu Province of China 12.2%.^{10–13} In analysis of various studies - forgetfulness being key factor for non-adherence in continuation phase of therapy. TB patients who were asymptomatic were more likely to discontinue the medication. As per a study conducted in Kolkata India, the urge to leave treatment once patient started feeling better, was a significant determinant of non-adherence to Anti TB medication¹²

78% persons who took part in the study were aware of their TREATMENT duration, while 22% were not. 25% of them or

roughly 1 out of 4 patients were not aware of the dangers of skipping/stopping their treatment without the doctor's advice. Approximately 20% patients said they did not feel any change since the initiation of the treatment and almost 33% of them received no support/persuasion by their family/friends to continue with DOTS medications. Major reasons for this behaviour as per patient's own admission were vomiting, general weakness, headache, lethargy, itching and skin rashes. For details please refer Table 1.

Finally non adherence to any chronic disease regimen as in our study is dependent upon interplay of various factors socio economic, literacy, empathy support of family members and employer towards patients, availability of health care facility to the patient, attitude and behaviour of health care provider. Lockdown restrictions during COVID-19 pandemic & fear of catching infection.

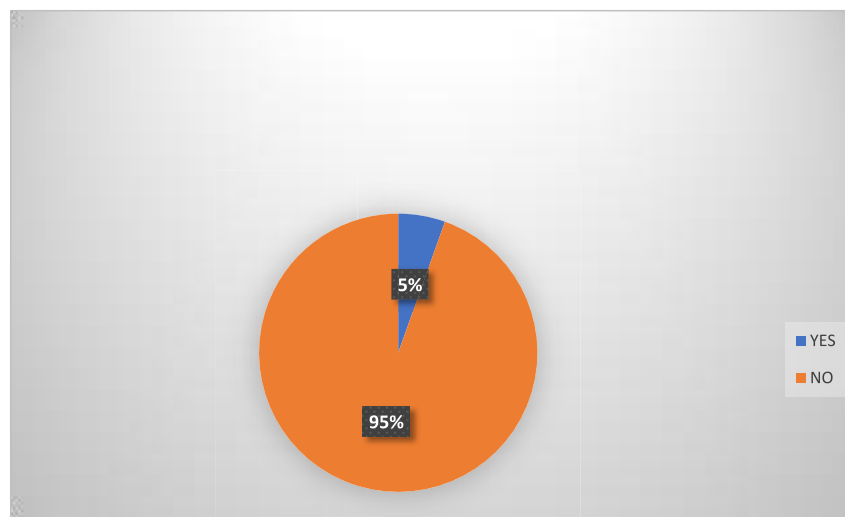
Promoting and hindering factors of non-adherence differ across the world and time to time. In given scenario. The study being cross sectional and hence had limitation of temporal relationship with some variables and won't be able to provide stronger causality.

4.1. Strength of study

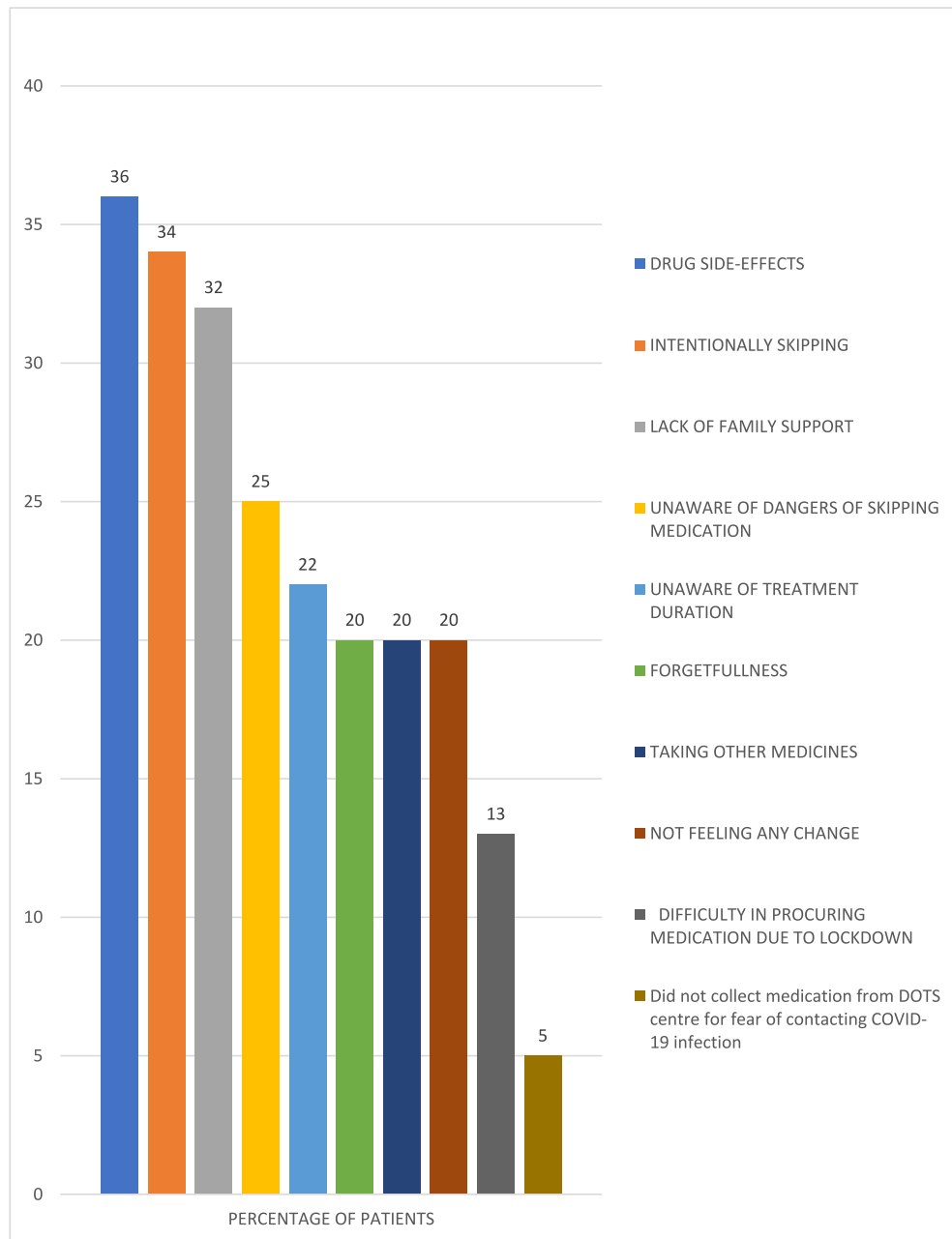
This is a pioneering work done to analyse the factors & reasons for non-adherence in COVID-19 pandemic in State of Chhattisgarh, Central India. This study will further strengthen the outcome & implementation of National Tuberculosis Elimination Programme.

4.2. Limitation of study

Short study duration.



Graph 3 – Shows whether patient didn't collect medication from TB centre for fear of contracting COVID-19 infection



Graph 4 – Shows various reasons for non-adherence in patients receiving anti-tubercular medication during COVID-19.

5. Conclusion

Non adherence is a complex phenomenon affected by the interplay of various modifiable and non-modifiable risk factors comprising of Human awareness, Socio-economic factors, family environment, etc. While previous studies on Tb non-adherence focussed more on the finding the percentage of patients who were non-adherent, we in our novel study aimed to find the reasons for the tubercular non-adherence and finding the contribution of all factors individually to non-adherence. The findings of our study being pioneering attempt in the state of Chhattisgarh, will enable the

meticulous development of facility to provide congenial atmosphere for the implementation of Anti-tubercular regimen & minimising non-adherence.

Major factors responsible for non-adherence are common to ours as well as various other studies before us and can namely be identified as drug side-effects, forgetfulness, being away from home, personal reasons, lack of family support and lacking knowledge about consequences of non-adherence, lockdown restrictions & fear of COVID (Table 4, Graph 4). Also, there is an overlap among various causal factors with more than one factor being responsible in a single patient.

The individual single biggest factors were Drug side -effects & intentionally skipping of medication. So, by

counselling/guiding the patients by making them aware of all the possible side-effects along with dangers associated with skipping the medication without doctor's advice can go a long way in improving patient compliance & reducing non-adherence. Also including patient's family members & friends in this process who ensure better compliance. Also, patient must be persuaded to continue with the treatment even if he/she isn't feeling any change and regular reminders be given to the patient to take the medicines on time. Last but not the least, if possible, all concomitant medication, unless deemed necessary, be stopped.

Conflicts of interest

The authors have none to declare.

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